REMARKS

I. Status of the Application

Claim 10 is pending in the application. New claims 13-28 have been added. Claim 10 stand rejected under 35 § U.S.C. 112, second paragraph as indefinite. Claim 10 stands rejected under 35 § U.S.C. 102(b) as anticipated by Cantor et al. (U.S. Patent No. 4,722,998).

Support for the newly added claims can be found in the specification and the claims as originally filed. Specifically, support for contacting cells with a culture medium for a sufficient time to produce a matrix can be found in the specification at least at page 2, lines 3-4. Support for active factors that are growth factors can be found in the specification at least at page 4, line 15. Support for growth factors that are bone formation factors, bone remodeling factors, cell proliferation factors and cell adhesion factors can be found in the specification at least at page 4, lines 15-16. Support for a mineralized matrix and a non-mineralized matrix can be found in the specification at least at page 2, lines 3-4. Support for bone marrow cells can be found in the specification at least at page 2, lines 23-24. Support for stromal cells can be found in the specification at least at page 2, lines 23-24. Support for autologous cells can be found in the specification at least at page 3, lines 12-14. Support for inducing differentiation by one or more inductors of differentiation can be found in the specification at least at page 2, lines 31-33.

Applicants have amended the specification and drawings to include a capital letter after the figure number for Figures 6A-C, as requested by the Examiner. Applicants respectfully request substitution and approval of submitted Figures 6A-C.

The Examiner states that the references listed on the IDS could not be located. Accordingly, Applicants are submitting herewith copies of the references originally supplied by Applicants in the parent cases (09/621,178 and 08/810,266).

The amendments presented herein add no new matter. Attached hereto is a marked-up version of the changes made to the claims captioned "Version of Amendments With Markings To Show Changes Made." Applicants respectfully request entry and consideration of the foregoing amendments, which are intended to place this case in condition for allowance.

II. Claim 10 Is Definite

At page 3, paragraph 1 of the instant Office Action, claim 10 stands rejected under 35 U.S.C. § 112, first paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner asserts that there is insufficient antecedent basis for the limitation "matrix." The Examiner further asserts that the phrase "such as" renders claim 10 indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. The Examiner also asserts that a broad range or limitation together with a narrow range or limitation is considered indefinite, and thus that the broad recitation "active factors" and the narrower recitation "growth factors" is indefinite.

Without acquiescing to the Examiner's rejection, Applicants respectfully submit that claim 10 has been amended to expedite prosecution. Claim 10 has been amended to recite an additional step wherein a matrix is formed, thus providing antecedent basis for the limitation "matrix." Claim 10 has further been amended to remove the language "such as growth factors," obviating the Examiner's assertions that the phrase "such as" is indefinite and that the claim has a broad range or limitation together with a narrow range or limitation. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

III. Claim 10 Is Novel Over Cantor et al.

At page 4, paragraph 2 of the instant Office Action, claim 10 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Cantor et al., U.S. Patent No. 4,722,998. The Examiner is of the opinion that Cantor teaches a method for isolating growth factors from the supernatant fluid obtained by incubation of T-cell lymphocytes (undifferentiated cells) in the presence of sheep red blood cells or concanavalin A and culture media. The Examiner asserts that the growth factors were purified by centrifuging the culture media and cells, and that the isolated factor was shown to act as a growth factor for T-lymphocytes, B-lymphocytes, mast cells, fibroblasts, and stem cells. The Examiner concludes that Cantor anticipates the instant claim. Applicants respectfully traverse this rejection.

Applicants respectfully submit that for a reference to anticipate a claim, the reference must teach each and every element of a claim. Amended claim 10 and claims depending therefrom are directed to a method of producing active factors comprising the steps of applying undifferentiated mammalian cells on a substrate, contacting the cells with a culture medium for a sufficient time to **produce a matrix**, contacting the cells with the culture medium for a sufficient time to produce active factors, removing the substrate and the matrix from the culture medium, and recovering the active factors from the culture medium.

Applicant's claimed method is directed to producing and recovering active factors in the context of matrix formation and growth. Such factors are capable of modulating bone formation, growth and remodeling (page 2, lines 12-13; page 4, lines 15-16). Applicant teaches that the active factors recovered as claimed are useful, for example, during implantation of load-bearing implants, spacers and bone fillers (page 2, lines 7-12; page 3, lines 7-8).

Cantor et al. fails to teach or suggest all of Applicant's claim limitations. Cantor et al. does not teach a method for the production of a matrix and active factors, wherein the matrix is

removed from contact with the culture medium and the active factors are recovered. Cantor et al. is instead concerned with producing factors that enhance and restore "the effectiveness of the immune system to resistance of disease," and in particular, growth factors produced by stimulated T-lymphocytes (abstract, column 1, lines 14-22). Cantor et al. teaches stimulating T-cells to produce growth factors by contacting T-cells with an antigen such as sheep red blood cells or a mitogen such as concanavalin A (abstract; column 2, lines 12-16). Specifically, Cantor et al. teaches producing T-cell clones (Example 1), stimulating cloned T-cell populations (Example 4), and characterizing growth factors present in the supernatants from the stimulated, cloned T-cells (Examples 4-12). Nowhere does Cantor et al. teach a method of producing active factors and producing a matrix on a substrate, as claimed by Applicant.

Therefore, Cantor et al. fails to teach each and every element of Applicant's claims. Accordingly, Applicant respectfully requests that the rejection of claim 10 under 35 U.S.C. § 102(b) as being anticipated by Cantor et al. be reconsidered and withdrawn.

III. Claims 13-28 Are Patentable Over Cantor et al.

New claim 20 and claims depending therefrom are directed to a method of producing bone growth factors comprising the steps of applying **bone marrow cells** on a substrate, contacting the bone marrow cells with a culture medium for a sufficient time to produce bone growth factors, and recovering the bone growth factors from the substrate. New claim 25 and claims depending therefrom are directed to a method of producing growth factors comprising the steps of applying **stromal cells** on a substrate, contacting the stromal cells with a culture medium for a sufficient time to produce growth factors, and recovering the growth factors from the substrate.

Cantor et al. neither teaches nor suggests methods of providing bone marrow cells to produce bone growth factors or methods of providing stromal cells to produce growth factors. As discussed above, Cantor et al. uses T-cells to isolate factors induced by T-cell stimulation. T-cells are not the same as bone marrow cells or as stromal cells. Bone marrow cells are hemopoietic cells (i.e., blood forming stem cells) that give rise to cells such as blood cells and bone osteoclasts (see exhibit A, first paragraph and page 3, last paragraph). Stromal cells are a specific type of bone marrow cell that give rise to collagen fibers and extracellular matrix components (exhibit A, first paragraph and page 3, last paragraph). Both of these cell types are located in the bone marrow and are capable of differentiating into bone cells. T-cells, however, are lymphocytes that develop in the thymus and are capable of differentiating into cytotoxic T-cells or helper T-cells upon stimulation (see exhibit B, page 1, last paragraph, page 2, third paragraph; exhibit C, page 1, third paragraph). T-cells do not differentiate into bone.

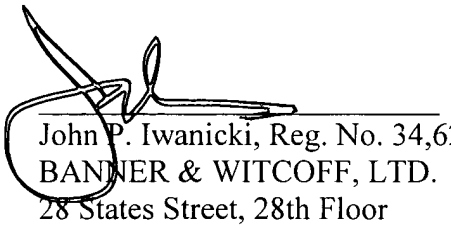
Thus, Cantor et al. fails to teach each and every element of Applicant's new claims. Accordingly, claims 13-28 are patentable over Cantor et al.

IV. Conclusion

Having responded to all outstanding issues, reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7111.

Respectfully submitted,

Dated: December 2, 2002



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Version of Amendments With Markings to Show Changes Made

In the Specification:

Please amend the specification as follows:

At page 12, lines 21 to 27:

Fig. [6a] 6A is a graph showing the DNA content (no. of cells) of a bone marrow cell culture on tissue culture polystyrene (- matrix) and in vitro formed bone matrix (+ matrix).

Fig. [6b] 6B is a graph showing the alkaline phosphatase activity (APA) of a bone marrow cell culture on tissue culture polystyrene (- matrix) and in vitro formed bone matrix (+ matrix).

Fig. [6c] 6C is a graph showing the APA/DNA ratio of a bone marrow cell culture on tissue culture polystyrene (- matrix) and in vitro formed bone matrix (+ matrix).

In the Claims:

Please amend the claims as follows:

10. (Amended) A method of producing active factors [such as growth factors,] comprising the steps of:

(a) applying undifferentiated mammalian cells on a substrate;

(b) contacting the cells with a culture medium for a sufficient time to produce a matrix;

[(b)] (c) [directly] contacting [said] the cells with [a] the culture medium for a sufficient time to produce [growth] active factors;

[(c)] (d) removing the substrate [with] and the matrix from the culture medium; and

[(d)] (e) recovering the active factors from the culture medium.